It is noted that the Examiner included with the office action of June 3, 2003 a copy of Applicants'previously submitted PTO Form 1449 which was previously submitted as part of an information disclosure statement and which lists references which were presented and considered during the prosecution of the parent application to this application, s.n. 09/033,996. Applicants note that the Examiner has not initialed the form evidencing that the specifically disclosed references have been considered by the Examiner. If the Examiner has found it difficult to get the copies of the disclosed references from the parent application, he should so note and Applicants will provide copies to the Examiner so that all the references are considered. Separately, Applicants have submitted a supplemental information disclosure statement dated March 2, 2004, which was not returned with the May 20, 2004 office action. Applicants respectfully request that the Examiner address the two previously submitted information disclosure statements so that the record accurately reflects that the cited documents have been considered. Should the Examiner wish to have copies of previously cited and submitted references, the Examiner is cordially requested to indicate same to the undersigned.

The Examiner has rejected the previously submitted claims variously under 35 U.S.C. §112, first and second paragraphs and §§102 and 103. Applicants shall address each of the Examiner's rejections in the sections which follow. For the reasons set forth in detail hereinbelow, Applicants respectfully submit that the present claims are patentable.

The §112, First Paragraph Rejection

The Examiner has rejected claims 1, 24-29 and 31 under 35 U.S.C. §112, first paragraph as being non-enabling for a therapeutic purine compound which has an azide moiety at a position in the purine other than the 6-position and other than a nucleoside or nucleotide analog at the 9 position of the purine base. Applicants respectfully traverse the Examiner's rejection inasmuch as the amended claims address the Examiner's concern. In particular, what is claimed is a pharmaceutical composition which comprises

a 6-azide substituted purine compound or a 6-azide substituted purine nucleoside or nucleotide compound, all of which are biologically active. It is respectfully submitted that the present specification enables this claim, inasmuch as one of ordinary skill in the art may readily determine a biologically/therapeutically active purine which has a 6-amine or 6-hydroxyl group. These compounds are well known in the art. Making the 6-azide substituted purine compounds as prodrug forms of these compounds is well within the routineer's skill, utilizing chemical steps which are essentially identical or analogous to those which are presented in the specification. For example, the 6-position of the purine group may contain a leaving group, such as a chloro or other leaving group (azido, etc.), which can be readily displaced using sodium azide or other nucleophilic azide. Alternatively, a leaving group may be displaced using hydrazine followed by exposing the hydrazine compound to sodium nitrite (see figure 5). These general synthetic approaches appear on pages 20-36 in the present specification and are readily adapted to numerous purines to produce 6-azide purines according to the present invention. Thus, the claimed invention is enabled from the teachings in the specification as well as the routine skills the practictioner brings to the problem of synthesizing 6-azido purine compounds according to the present invention. None of the steps which are set forth and described in the specification are onerous or difficult- in fact, these synthetic steps are rather routine.

With respect to the enzymatic conversion of the 6-azido group to the corresponding 6-amino or 6-hydroxy, it is respectfully submitted that the enzymatic conversion of this moiety is very general and applicable to the present invention. The conversion of the 6-azido group to the 6-amino group occurs in the liver and the reductase enzyme which is responsible for this conversion is structurally non-specific and is readily adaptable to a large number of compounds. This is explained in the specification generally and specifically in the first full paragraph on page 15. It is fully expected that the azide compounds will be readily converted to their corresponding amino analogs. The 6-amino group may thereafter be converted to a 6-hydroxy group by a deaminase enzyme. Notwithstanding that an enzymatic conversion takes place, these

reactions and conversions are all quite non-specific pursuant to normal drug metabolism which occurs primarily in the liver. Thus, it is respectfully submitted that practicing the instantly claimed invention is well within the skill of the routineer. Undue experimentation is not required to practice the present invention.

Notwithstanding the sufficiency of the teachings of the specification, there will nonetheless be some measure of routine experimentation required to adapt the general synthetic methods disclosed in the present specification to all aspects of the present invention. However, given the straightforward nature of the identification and synthesis of the claimed compositions and the general applicability of enzymatic conversion of prodrugs to active compounds pursuant to typical drug metabolism in the patient's liver, there is simply no fair way of characterizing such effort as involving undue experimentation. Consequently, it is respectfully submitted that the presently presented claims meet the requirements of 35 U.S.C. §112, first paragraph.

The §112, Second Paragraph Rejection

The Examiner has rejected claims 29-31 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. In particular, the Examiner is concerned that the originally filed claim 29 reads on a dangling valence when R_2 is O. In order to address the Examiner's rejection, Applicants have amended claim 29 such that R_2 is OH, not O. It is respectfully submitted that this modification addresses the Examiner's concerns.

The §102 Rejection

The Examiner also has rejected claims 1 and 24-27 as being anticipated by Bauman, et al., U.S. patent no. 5,180,824 ("Bauman"). The Examiner cites Bauman for disclosing the utilization of 6-azido-2-fluorpurine as an intermediate in the synthesis of

fludarabine, fludaravine phosphate and related nucleoside pharmacological agents. The Examiner contends that Bauman's disclosure of 6-azido-2-fluorprine (compound 5) anticipates the instantly claimed purine compounds. Bauman further discloses the reduction of the azide to an amine. Applicants respectfully traverse the Examiner's rejection.

The instant invention is directed to a pharmaceutical composition adapted for delivery to a subject comprising the compounds which are set forth in the claims in combination with a pharmaceutically acceptable carrier. Thus, the present invention acknowledges the discovery of 6-azidopurine compounds as claimed as prodrug forms of their corresponding 6-amino and 6-hydroxy purine analogs. Bauman does not anticipate the present invention because Bauman fails to provide a pharmaceutical composition. Rather, the compound which Bauman does disclose is recognized as an intermediate in the synthesis of other compounds which are taught to exhibit biological activity. Bauman does not disclose a relevant intermediate in combination with a pharmaceutical carrier because Bauman failed to recognize the utility of the disclosed compound as anything other than a chemical intermediate to synthesize biologically active compounds. Note also that Bauman discloses a chemical reduction of the 6-azido derivative to produce the target compounds. Because Bauman does not disclose all of the elements of at least one of the claims of the present application, Bauman does not anticipate the present invention.

The §103 Rejection

The Examiner rejects claims 1 and 24-28 under 35 U.S.C. §103(a) as being unpatentable over Bauman in combination with Gmeiner, et al. U.S. patent no. 5,457,187 ("Gmeiner"). The Examiner cites Bauman for teachings the utilization of 6-azido-2-fluorpurine (a 6-azido purine) as an intermediate for the synthesis of fludarabine, fludarabine phosphate and related nucleoside pharmacological agents. The Examiner further cites Bauman for teaching the reduction of the azide to an amine. The Examiner

concludes from the teachings of Bauman that it is obvious to produce 6-azidopurine compounds according to the present invention. The Examiner cites Gmeiner for teaching the delivery of homo-oligomeric nucleotides to confer several distinct advantages relative to their delivery as nucleoside bases. From this and related teachings, the Examiner concludes that the present invention is obvious over the teachings of Bauman, which discloses azidonucleoside derivatives as synthetic chemical intermediates and Gmeiner which discloses the desirability of employing nucleotides or oligonucleotides without reference to the inclusion of an azido moiety within the active compound. Applicants respectfully traverse the Examiner's rejection. Applicants respectully submit that the teachings of the art in no way suggest that 6-azidopurine compounds could be effective prodrug forms of biologically active 6-amino or 6-hydroxyl purine compounds including nucleosides and nucleotides.

The present invention relates to pharmaceutical compositions adapted for delivery to a subject comprising a prodrug 6-azidopurine compound as claimed in combination with a pharmaceutically acceptable carrier. A combination of the teachings of Bauman and Gmeiner do not render the claimed invention obvious. First, as discussed above, Bauman discloses 6-azidopurine compounds as being useful as chemical *intermediates* useful in the chemical synthesis of nucleoside compounds which have biological activity. There is no disclosure in Bauman of any biological activity of the 6-azidopurine intermediates or that those intermediates could be effective prodrug forms and could lead to biological activity other than through a chemical synthesis which results in a biologically active compound(s). However this is decidedly not the present invention. The chemical intermediates of Bauman are not disclosed for use as pharmaceutical compounds and Bauman clearly fails to recognize the 6-azidopurine compounds as prodrug forms given that there is absolutely no recognition of an enzymatic conversion of the azido functionality to an amine or hydroxyl functionality. Although Bauman teaches a reduction (chemical hydrogenation) of the 6-azido group to a 6-amino group, this occurs via a purely chemical hydrogenation process. Moreover, Bauman does not even obliquely suggest or recognize the desirability of the 6-azido group because it can be used

as a prodrug form converted by liver enzymes to the corresponding 6-amino or 6-hydroxy compound. Indeed, Bauman fails completely to disclose or suggest the present invention.

Turning to Gmeiner, this reference does absolutely nothing to obviate the deficiencies of Bauman. Whereas Bauman discloses a 6-aminopurine compound as a chemical intermediate for the production of biologically active purine nucleoside analogs, Gmeiner does nothing to add to deficient disclosure of Bauman. Instead, Gmeiner is directed to chemotherapeutic treatments and methods for increasing the in-vivo half-life and target specificity of chemotherapeutic drugs. While it may be true that Gmeiner teaches that the oligomeric compounds may be oligonucleo*tides* (i.e., containing phosphate groups), there the similarity with the present invention ends. There is no disclosure in Gmeiner that 6-azido groups on the compounds according to the present invention or any compound for that matter may function as effective prodrug forms precisely because of the existence of that azido group. Instead, Gmeiner speaks to the use of a phosphate group on oligomric 5-fluorouridine as serving some purpose related to enhanced half-life of the oligomeric compound.

Combining the teachings of Bauman and Gmeiner does not render the present invention obvious. If anything, a combination of Bauman and Gmeiner teaches *at best* that it may be appropriate to phosphorylate the 5'-hydroxyl position of the sugar synthon of a nucleoside analog in order to make the nucleoside analog have a better half-life *in vivo*. However, Gmeiner does not provide any teaching or suggestion to obviate the intellectual hurdle created by the teachings of Bauman that a 6-azido group on a purine base is an effective chemical intermediate on the way to biological compounds using chemical synthetic means, but ***not*** an effective prodrug for a 6-amino or 6-hydroxy purine compound. There is no absolutely no teaching or suggestion in Bauman that the relevant compound is even biologically active. In short, the teachings of Bauman and Gmeiner do not render the present invention obvious.

In light of all of the foregoing, it is respectfully maintained that the instant amendments and remarks address all of the grounds for rejection raised by the Examiner. Accordingly, Applicants respectfully maintain that all of the pending claims should be passed to issue. No fee is due for the presentation of this amendment A petition for an extension of time of one month was previously submitted as was a check in the amount of $55. If any additional fee is due or any overpayment has been made, please debit/credit deposit account no. 04-0838. Should the Examiner wish to discuss the instant application in an effort to discuss allowance of the application, he is cordially requested to telephone the undersigned at the number set forth below.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on November 5, 2004.

Henry D. Coleman (Reg. No. 32,559)